

REMARKS

On April 22, 2010, Applicants submitted a Notice of Appeal and a request for a two month extension of time for responding to the final Office Action of November 24, 2009. Rather than pursue the appeal at this time, Applicants wish to address the Examiner's comments and amend claim 21 as a matter of clarity. Applicants have also now submitted new claim 39 to recite the preferred embodiment wherein expression of the controlled ribosomal protein gene is prevented and new claim 40 to recite the embodiment wherein the inducible promoter is adjacent to the non-heterologous ribosomal protein gene.

In the response to the Office Action of November 24, 2009, Applicants have amended claim 21 to recite that the claimed attenuated live parasite comprises a non-heterologous ribosomal protein gene under the control of an inducible promoter, by which ribosomal protein synthesis is limited, which limits parasite replication in infected cells. Support for this amendment is found in the specification, for example, on page 6, lines 1-10.

In the Office Action of November 22, 2009, the Examiner rejected claims 21-35 under 35 USC 112, second paragraph, for being indefinite. The Examiner questioned the meaning of "a ribosomal protein gene of said parasite." Applicants believe the meaning is clear, that it is a gene of the parasite, not a heterologous gene. To assure clarity, however, Applicants have amended the claim to recite that the gene is a "non-heterologous ribosomal protein gene."

Claims 21, 28-32 and 34-35 stand rejected under 35 USC 103(a) for being obvious over Titus et al. in view of Yan et al. Titus et al. is relied on for teaching the development of a safe live attenuated Leishmania vaccine, but does not teach a ribosomal protein gene under the control of an inducible promoter. Yan et al. is said to teach tetracycline regulated gene expression in Leishmania, wherein the inducer TetR binds to TetO operator to suppress transcription from the adjacent promoter. The Examiner concluded that Yan et al. teach a promoter that can be switched on and off, regulating the expression of ribosomal protein genes by inhibiting transcription, whereby ribosome synthesis is limited, thereby limiting replication in infected cells. Applicants do not agree that this is taught by Yan et al.

USSN: 10/526,731

Attorney Docket: 2002.017 US

Response to Office Action of November 24, 2009

The rejection over Titus et al. in view of Yan et al. is respectfully traversed. The present invention is the control of ribosomal protein production by controlling ribosomal gene expression. Ribosomal proteins are necessary for parasite replication. With the present invention, the inducible promoter regulates the expression of the ribosomal protein gene, which controls the production of ribosomal proteins. In the absence of all ribosomal proteins, ribosomes are not produced. Ribosomes are necessary for parasite replication. With the promoter switched off, the parasite can infect a cell and, to the extent ribosomes are already present, replicate. However, with no further ribosome synthesis, parasite replication is limited by the ribosomes already present. None of the prior art suggests an organism in which ribosome synthesis is controlled by controlling expression of the ribosomal protein gene with an inducible promoter.

Applicants define ribosomal proteins as proteins that are used to form the ribosome itself (Specification, page 6, lines 1 and 2). By contrast, Yan et al. discloses inserts in the Tubulin or in the ribosomal RNA gene region, not the ribosomal protein gene region. There is no relationship to ribosomal protein synthesis. Tubulin proteins form microtubular filaments in a cell's cytoplasm, which function in stabilizing the cell and transporting molecules and structures through the cell. It is not part of a ribosome. Contrary to the Examiner's statement on page 4 of the Office Action, Yan et al. do not teach regulating the expression of ribosomal protein genes.

This deficiency is not made up by Titus et al., which discloses the use of the Tet-operon to control gene expression in *Leishmania*, based on the presence or absence of thymidine. It does not suggest anything relating to an attenuated parasite for which replication is controlled by controlling ribosomal protein expression.

Claims 21, 28-32 and 34-35 stand rejected under 35 U.S.C. § 102(b) for anticipation by Wirtz et al. It has been asserted that Wirtz et al. teach the inducible expression of transgenes including ribosomal protein genes in *Trypanosome*.

The rejection over Wirtz et al. is respectfully traversed. Applicants respectfully submit that Wirtz et al. simply does not teach the regulation of ribosomal protein genes. It instead teaches the regulation of heterologous genes. Although the heterologous gene may be inserted in the

USSN: 10/526,731

Attorney Docket: 2002.017 US

Response to Office Action of November 24, 2009

vicinity of the ribosomal RNA genes, they are not themselves regulated. More importantly, the ribosomal genes addressed in this reference code for ribosomal RNA, they are not translated to encode any ribosomal proteins. In the *Leishmania* genome of Wirtz et al, the ribosomal protein genes are located in a different section of the genome from that wherein the heterologous genes are taught to be inserted. Consequently, there is no regulation of a ribosomal protein gene suggested by Wirtz et al. As set forth above, Applicants have made clear their meaning of “ribosomal proteins,” they are, exclusively, proteins that form the ribosome itself. (Specification, page 6, lines 1-2). They do not include ribosomal RNA.

Claims 21-27 and 29-31 stand rejected under 35 U.S.C. § 103(a) for obviousness over Sutherland et al. in view of Durocher and further in view of Gozar et al. Sutherland et al. is said to teach the attenuation of *Theileira* cell lines and other avirulent Apicomplexan protozoa and the desire and need to control gene expression in such parasites. It is said, however, that Sutherland et al. did not teach that the parasites comprised a ribosomal protein gene under the control of an inducible promoter. Durocher and Gozar et al. are said to teach that an inducible system advantageously provides stringent regulation of gene expression in prokaryotes.

The rejection over Sutherland et al. taken with Durocher and Gozar et al. is respectfully traversed. Applicants respectfully submit that there is no suggestion of controlling ribosomal protein expression in a parasite with a gene under the control of an inducible promoter. There is no suggestion of an attenuated live parasite that can be limited in its replication in infected cells by having ribosome synthesis controlled through the regulation of the expression of ribosomal protein genes.

Southerland et al. describe attenuation by in-vivo passaging. It describes attenuated parasites, nothing more. Durocher describes an inducible promoter system that can be used to induce expression of a desired gene. Gozar studied the expression of a ribosomal RNA gene.

Applicants agree the cited references disclose that attenuated parasites are known and that controlling gene expression is known. But creating an attenuated parasite with an inducible promoter regulating the expression of a ribosomal protein gene is neither disclosed nor suggested in the prior art. Attenuating the virulence of an organism is not new, but attenuating the

USSN: 10/526,731
Attorney Docket: 2002.017 US
Response to Office Action of November 24, 2009

virulence by controlling the expression of a ribosomal protein gene is neither disclosed nor suggested. Nothing in the cited art suggests a parasite with inhibited ribosomal protein gene expression that would be an effective immunogen with limited replication, and therefore limited virulence, without danger of reverting to wild type.

In view of the above, with the present amendments to claim 21 and the addition of claims 39 and 40, it is believed that the application is in condition for allowance. Favorable action is solicited.

Should the Examiner believe that a conference would be helpful in advancing the prosecution of this application, she is invited to telephone Applicants' attorney at the number below.

Applicants do not believe that any other fee is due in connection with this filing. If, however, Applicants do owe any such fee(s), the Commissioner is hereby authorized to charge the fee(s) to Deposit Account No. **19-0365**. In addition, if there is ever any other fee deficiency or overpayment under 37 C.F.R. §1.16 or 1.17 in connection with this patent application, the Commissioner is hereby authorized to charge such deficiency or overpayment to Deposit Account No. **19-0365**.

Respectfully submitted,

/William M. BLACKSTONE, Registration No. 29,772/

William M. Blackstone, Registration Reg. No. 29772
Office of the General Counsel-Merck & Co., Inc.
Intellectual Property-Animal Health
Schering-Plough Corp.
Law Dept. K-6-1, 1990
2000 Galloping Hill Road
Kenilworth, NJ 07033
(tel) 410 464 0491